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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/776,874	02/06/2001	Iris Pecker	01/21603	8407

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EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	14

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/776,874	PECKER ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants amendment of the specification, claims 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 40, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62 and 64 and the addition of new claims 66-70, Paper No. 13, 4/21/2003, is acknowledged. It is noted that previous to the listing of each of the fore mentioned amended claims (top of page 3) applicants recite "Please amend claims 14, 44, 46, 48, 50 and 52 as follows:", however recitation is interpreted as a mistake since applicants actually amended the claims as stated above and also show a marked-up copy of these claims.

Claims 14-70 are still at issue and are present for examination.

Applicants' arguments filed on 4/21/2003, Paper No. 13, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-33, 44-65, 66, 67 and 69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Newly amended claims 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 40, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64 and 66 are each indefinite in that the recitation "a polypeptide at least 60% homologous to at least one of SEQ ID NOs: 10, 14, or 44 or portions thereof,". First applicants are reminded of the earlier restriction requirement, Paper No. 8, 7/2/2002, as well as applicants election, Paper No. 9, 8/1/2002, in which applicants elected the prosecution of those polypeptides drawn to SEQ ID NO: 10, not SEQ ID NOs: 14 or 44. And second it is unclear as to applicants intention in limiting the claimed polypeptide to a specific SEQ ID NO:, such as SEQ ID NO: 10, or a portion thereof. What is encompassed by those polypeptides having 60% homology to a portion of SEQ ID NO: 10? For the purpose of advancing prosecution the above referred to recitations in these claims is interpreted as "a polypeptide at least 60% homologous to at least one of SEQ ID NOs: 10, 14, or 44 or portions thereof,".

Claim 69 is indefinite in the recitation of "hybridizing" as this term is unclear absent a statement of the conditions under which the hybridization reaction is performed. Nucleic acids which will hybridize under some hybridization conditions will not necessarily hybridize under different conditions.

The previous rejection of claims 18, 19, 28, 29, 38, 39, 48, 49, 58 and 59 as being indefinite in that the recitations "CXC chemokine" and "PAI1" is hereby withdrawn, however, it is suggested that the first time applicants use the term PAI1 in a claim and specification, since this is an abbreviation, applicants spell out the abbreviated phrase in full prior followed by the abbreviation in parenthesis.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 68-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The previous rejection of claims 14-33 and 44-65 has been withdrawn based on applicants amendment .

Newly added claims 68-70 are directed to all possible preparations comprising a recombinant protein having heparanase catalytic activity or being cleavable so as to acquire said heparanase catalytic activity, wherein said preparation is free of non-heparanase polypeptides encoded by human nucleic acid sequences and said polypeptide has a pair of glutamic acid residues participating in its active site (claim 68), all possible preparations comprising a recombinant protein having heparanase catalytic activity or being cleavable so as to acquire said heparanase catalytic activity, wherein said wherein said recombinant protein includes a polypeptide capable of being encoded by a polynucleotide capable of hybridizing to at least a portion of SEQ ID NO: 9 (claim 69), all possible preparations comprising a recombinant protein having heparanase catalytic activity or being cleavable so as to acquire said heparanase catalytic activity, wherein said wherein said protein is characterized by being about 50 or about 65 kDa and capable of being purified by the specified protocol (claim 70).

As previously discussed for claims 14-33 and 44-65, the specification, however, only provides a single representative species isolated of such preparations and pharmaceutical compositions comprising said preparation wherein the protein having heparanase catalytic activity has the amino acid sequence of SEQ ID NOs: 10, 14 or 44, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional representative species of these preparations, compositions or proteins by any identifying structural characteristics or properties other than the activities recited in claims, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 14-63 and 68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants previous amendment to claims 14-63 which recite "the preparation being free of non-heparanase polypeptides encoded by human nucleic acid sequences" (claims 14, 15, 24, 24, 34, 35, 44, 45, 54, 55 and 68), "... said isolated protein being substantially devoid of glycosilation..." (claims 16, 17, 26, 27, 36, 37, 46, 47, 56 and 57), "...the preparation being substantially free of a CXC chemokine or PAI1" (claims 18, 19, 28, 29, 38, 39, 48, 49, 58 and 59), "...said isolated protein characterized by insect cell derived sugar prosthetic groups..." (claims 20, 21, 30, 31, 40, 41, 50, 51 60 and 61), or "...said isolated protein characterized by non-human cell derived sugar prosthetic groups..." (claims 22, 23, 32, 33, 42, 43, 52, 53, 62, and 63), are not supported by the original disclosure and therefore considered new matter.

Applicants traverse this rejection on the basis that the Written Description Guidelines clearly state that "there is no *in haec verba* requirement", such that the wording of the new or amended claims does not need to be literally present in the specification, but rather it is sufficient that the wording is supported in the specification through express, implicit, or inherent disclosure. Applicants submit that each of the above limitations have clear support in the specification and as an example applicants expand their analysis of why the specification supports the limitation that recites "the preparation being free of non-heparanase polypeptides encoded by human nucleic acid sequences". Applicants argument is not found persuasive, because using such an analysis does not justify support for the above limitations. Just because the recited limitation is a property of a recombinant protein produced by a particular method, does not support a claim to such a property. Applicants did not contemplate the claimed

limitation/ subgenus at the time of filing, and hence the inclusion the above limitations limiting the claims to the above referred to sub-genuses is considered new matter.

Claims 14-33, 34-43, 44-65 and 66-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a protein or preparation comprising said protein having the amino acid sequence of SEQ ID NO: 10, said protein having heparanase activity or being so cleavable so as to acquire said heparanase activity, does not reasonably provide enablement for any protein or preparation comprising said protein having heparanase activity or being so cleavable so as to acquire said heparanase activity, regardless of whether said protein is about 50 or about 65 kDa, has a pair of glutamic acids participating in its active site, or capable of eliciting anti-heparanase antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection was previously made for claims 14-33 and 44-65. Claims 34-43 were mistakenly left out of the previous rejection but they should have been included. Further newly added claims 66-70 are also included in this rejection. For applicants convenience the previous rejection is repeated below with the inclusion of claims 34-43.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of

direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 14-33, and 44-65 are so broad as to encompass any protein or preparation comprising said protein having heparanase catalytic activity or being cleavable so as to acquire said heparanase catalytic activity, and pharmaceutical compositions comprising said preparation, wherein said protein or preparation is free of non-heparanase polypeptides encoded by human nucleic acid sequences" (claims 14, 15, 24, 24, 44, 45, 54 and 55), wherein said isolated protein is substantially devoid of glycosilation (claims 16, 17, 26, 27, 46, 47, 56 and 57), wherein the preparation is substantially free of a CXC chemokine or PAI1 (claims 18, 19, 28, 29, 48, 49, 58 and 59), wherein said isolated protein is characterized by insect cell derived sugar prosthetic groups (claims 20, 21, 30, 31, 50, 51 60 and 61), wherein said isolated protein is characterized by non-human cell derived sugar prosthetic groups (claims 22, 23, 32, 33, 52, 53, 62, and 63), wherein said protein is at least 60% homologous to at least one of SEQ ID NOs: 10, 14, or 44 or portions thereof (claims 14-33 and 44-65). Claims 34-43 are so broad as to encompass any preparation comprising a protein having at least 70% homologous to SEQ ID NO: 10, said protein having heparanase catalytic activity or being cleavable so as to acquire said heparanase catalytic activity, with various of the above recited limitations and pharmaceutical compositions comprising said preparation.

Claims 66-70 included in the rejection for the same reasons as stated with respect to claims 14-33 and claims 44-65.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins, preparations and pharmaceutical compositions comprising said preparations, broadly encompassed by the claims, including all proteins or preparation comprising said proteins wherein said protein has heparanase activity or is so cleavable so as to acquire said heparanase activity. The claims rejected under this section of U.S.C. 112, first paragraph, do not place minor if any structural limits on the claimed protein. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to that protein and preparation comprising said protein wherein said protein has the amino acid sequence of SEQ ID NO: 10, 14 or 44.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is

unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any protein having heparanase catalytic activity and a mere 60% homology to SEQ ID NO: 10, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting heparanase catalytic activity; (B) the general tolerance of heparanases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a heparanase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the heparanase catalytic activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those proteins of the claimed genus having the claimed heparanase catalytic activity.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated

with the scope of the claims broadly including any number of amino acid modifications of any heparanase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants traversal of the previous rejection of claims 14-33 and 44-65 based on a lack of enablement is intermixed with applicants traversal of the rejection of claims 14-33 and 44-65 based on a lack of written description. Applicants appear to traverse this rejection on the basis that the mere limitation of the rejected claims to the genus of those polypeptides comprising at least 60% homology to SEQ ID NO: 10 in combination with the functional limitation having heparanase activity is sufficient in overcoming this rejection. This argument is not found persuasive because as stated above Because of the lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the heparanase catalytic activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable, it would require undue experimentation for one skilled in the art to arrive at the majority of those proteins of the claimed genus having the claimed heparanase catalytic activity 60% homology to SEQ ID NO: 10.

It is further noted that claims 68-70 have no structural limitations of the claimed polypeptides.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 64, 65, 66, 67, 69 and 70 are rejected under 35 U.S.C. 102(b) as being anticipated by Fuks et al. (U.S. Patent No. 5,362,641).

The rejection was stated in the previous office action as it applied to previous claims 64 and 65. Applicants have amended claims 64 and 65 and added new claims 66, 67, 69 and 70 and traverse the rejection of claims 64 and 65.

Applicants traverse this rejection on the basis that the "the antibody of Fuks cannot anticipate claims 64 and 65, as the antibody of claims 64 and 65 recognizes heparanase, while that of Fuks does not. This argument is not found persuasive because the rejected claims are drawn to a protein not an antibody and irrespective of any antibody prepared and isolated by Fuks, the protein of Fuks is capable of eliciting an anti-heparanase antibody. Just because Fuks reportedly were unsuccessful in generating an antibody does not change this inherent limitation of the protein taught by Fuks.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
June 27, 2003